114. The method of claim 113, wherein the nucleic acid encoding the antigen is administered to the individual or test system concurrently with the immune adjuvant composition.

115. The method of claim 113, wherein the nucleic acid encoding the antigen is administered before the immune adjuvant composition.

116. The method of claim 113, wherein the nucleic acid encoding the antigen is administered after the immune adjuvant composition.

REMARKS

Claims 49-61, 79, and 84-89 have been canceled without prejudice. Applicant has canceled claims 49-61 and 84-89 because, according to the Examiner, the subject matter is not within the scope of the election made on November 3, 2000 in response to the Restriction Requirement issued on October 3, 2000. Applicant reserves the right to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part, or divisional applications. Claims 19-28, 63-78, 80-83, and 90-116 are pending. Claims 25-26, 63-77, and 80 have been amended to more particularly point out and distinctly claim the invention in order to place the claims in condition for allowance. New claims 90-116 have been added. The subject matter of the new and amended claims is fully supported in the specification. No new matter has been added. For example, support for amended claims 65 and 73 is on page 6, lines 8-17. Support for amended claims 25-26, 65-66, 75, and 77, is on page 9, line14 to page 10, line 9 and page 11, lines 12-17. Support for amended claims 64, 67, 68, 70, 72, 74, 76, and 77 is on page 14, line 22 to page 15, line 4. Support for new claims 100-102 is on page 10, lines 13-16. Support for new claims 90-99 and 103-112 is on page 3, lines 13-15; on page 5, line 21 to page 6, line 7; page 8, line 9 to page 9, line 2. Support for new claims 113-116 is on page 18, lines 9-11.

A marked up versions of the amended claims showing the amendment is attached hereto as Exhibit A. Matter that has been deleted is indicated by brackets and matter that has been added is indicated by underlining. A copy of the claims as pending after entry of the foregoing amendment is attached as Exhibit B. Applicant respectfully

requests entry of the amendments and remarks made herein into the file history of the present application.

A. The Specification

The amended paragraph filed on January 18, 2002 in the Amendment Under 37 C.F.R. § 1.111 is objected to under 35 U.S.C. § 132 as allegedly introducing new matter into the disclosure. The Examiner points out that the specification as filed stated that the oligonucleotide of the invention may be 5-40 base pairs in length (see *e.g.*, page 8, lines 14-15 of the specification as filed). Accordingly, the Examiner contends that Applicant's amendment to the specification to recite a lower limit of 4 nucleotides for the oligonucleotide of the invention constitutes new matter. Applicant respectfully disagrees.

The specification as filed discloses an embodiment of the present invention that recites an immunostimulatory oligonucleotide which contains a CpG motif having the formula $5'X_1CGX_2 3'$ (see *e.g.*, page 8, lines 19-22 of the instant specification). Additionally, claims 27 and 57 as originally filed (see page 27, lines 1-4 and page 30, lines 7-10 of the instant specification) recite the lower limit of 4 nucleotides. The M.P.E.P. § 608.01(l) states:

> In establishing disclosure, applicant may rely not only on the description and drawing as filed but also on the original claims if their content justifies it. Where subject matter not shown in the drawing or described in the description is claimed in the application as filed, and such original claim itself constitutes a clear disclosure of this subject matter, then the claim should be treated on its merits, and requirement made to amend the drawing and description to show this subject matter. The claim should not be attacked either by objection or rejection because this subject matter is lacking in the drawing and description. It is the drawing and description that are defective, not the claim.

Thus, in view of M.P.E.P. § 608.01(l), Applicant's amendment to the specification is proper and should be entered.

B. Rejections Under 35 U.S.C. § 112

1. The Rejection Under 35 U.S.C. § 112, first paragraph

Claims 73-74 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that

the specification does not disclose an immunostimulatory oligo that is 4-40 base pairs in length. Applicant has amended the specification to reflect the lower limit of 4 nucleotides. Because this amendment does not constitute new matter (for reasons discussed previously, see section A *supra*), the amendment should be entered. Thus, the specification does indeed describe the claimed subject matter by reciting that the immunostimulatory oligo of the invention is 4-40 base pairs in length.

Claims 49-62, 64, 67, 68, 70, 72, 74, 76, 77, 79, and 87-89 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable a person skilled in the art to use the invention commensurate in scope with the claims. The Examiner contends that the specification does not reasonably provide enablement for merely administering a saponin and a nucleic acid sequence comprising at least one unmethylated CpG without also administering a nucleic acid sequence encoding an antigen. In response, Applicant has amended claims 64, 67, 68, 70, 72, 74, 76, and 77 to recite that an antigen encoded by a nucleic acid is also administered to the individual or test system. Applicant notes that claims 49-61 and 84-89 have been canceled as being outside of the scope of the elected invention.

2. <u>The Rejections Under 35 U.S.C. § 112, second paragraph</u>

Claims 19-32, 49-62, 73-74, 84, and 87 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Claims 19-32 and 49-62 are said by the Examiner to be indefinite because the metes and bounds of the CpG motif being claimed are allegedly unclear. The immune adjuvant composition in claim 19 comprises at least 2 components -- namely a saponin adjuvant and an immunostimulatory oligonucleotide comprising one or more CpG motifs. Claim 19 recites that the immunostimulatory oligonucleotide is not a part of a DNA vaccine vector. With this exception, the claimed immunostimulatory oligonucleotide can be any oligonucleotide that contains a CpG motif, and is defined in the specification as an oligonucleotide that comprises at least one unmethylated CpG dinucleotide and stimulates an immune response. See Specification, page 2, lines 3-10. A CpG motif, as defined in the specification, can be from 4-40 base pairs in length, and is a stretch of DNA containing at one or more CpG dinucleotides. See Specification, page 8, lines 12-22. According to the present claims, the immunostimulatory oligonucleotide of the presently claimed invention is

not part of a DNA vaccine vector, although it could be a part of vector that is not a DNA vaccine vector. As such, Applicant contends that immunostimulatory oligonucleotide is described sufficiently.

Claims 84 and 87 are allegedly indefinite because, according to the Examiner, the Markush group is improper. Applicant has canceled claims 84 and 87.

Claims 73-74 are allegedly indefinite because, according to the Examiner, it is unclear if the nucleic acid sequence comprising a CpG motif being claimed is from 4-40 base pairs or from 4-40 base pairs or greater. Furthermore, the claims are said to be indefinite because it is allegedly unclear if "comprising at least one unmethylated CpG motif" refers to the 4-40 bases or the oligo. The Examiner has suggested language that would overcome the rejection. Accordingly, pursuant to the Examiner's suggestion and without in any way conceding that the claim as written is unclear, for the sole purpose of expediting prosecution of this application and with fully reserving our rights to prosecute this subject matter in a subsequent patent application, Applicant has amended claim 73 to recite the Examiner's suggested language. Thus, as amended, the claim is not indefinite.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 112.

C. Rejections Under 35 U.S.C. § 102

1. Rejections Over Urban and Sasaki

Claims 65, 67, and 75-77 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 6,013,258 ("Urban") as supported by Krieg et al., 1998, *Trends in Microbiology* 6:23-26 ("Krieg") and United States Patent No. 5,808,024 ("Sasaki") as supported by Krieg. Applicant respectfully disagrees.

The Examiner contends that the limitation of a modified oligonucleotide is equivalent to the plasmid of Urban or Sasaki because the CpG sequences are part of a plasmid that has been genetically engineered. Additionally, the Examiner contends that the limitation of a chemically modified saponin is equivalent to either QuilA which has been added to cholesterol (as in Urban) or QS-21 which has been purified from saponin (as in Sasaki). Although Applicant maintains the belief that one of ordinary skill in the art understands the term "modified" as used in the above-mentioned claims and in the present specification to be a chemical modification that alters the structure of the nucleotide or saponin, the claims have been amended solely to further prosecution. As such, the claims

now recite the term "non-traditional". As used in the present specification, the term "non-traditional," when used to describe a nucleic acid or saponin adjuvant, refers to a change of the chemical structure of the nucleic acid or saponin adjuvant. See Specification, page 9, lines 14 to page 10, line 9. Thus, for example, a recombinant nucleic acid that has exclusively phosphodiester linkages and the typical A. T, G and C purines and pyrimidines would not be considered a "non-traditonal" nucleic acid as that term is used in the specification, since the building blocks of such a recombinant nucleic acid (the bases and the linkages) are the typical, "traditional" ones.

Thus, an immunostimulatory oligonucleotide comprising one or more "non-traditional" nucleotides is not equivalent to an oligonucleotide in which has been genetically altered (as in recombinant DNA technology). In the former, one or more of the nucleotides is altered in comparison to traditional nucleotides. This is in contrast with recombinant DNA where the nucleotides are traditional albeit assemble in an altered order. Similarly, a "non-traditional" saponin adjuvant is not equivalent to a traditional saponin that has been mixed with another component (as with QuilA and cholesterol) or purified (as with QS-21). In the latter cases, the saponin itself remains traditional although the components surrounding it may be altered. Therefore, neither Urban nor Sasaki discloses or suggests an immunostimulatory oligonucleotide comprising one or more "non-traditional" nucleotides or "non-traditional" saponins.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 102.

2. <u>The Rejection Over Agrawal</u>

Claims 19-20, 24-27, 29-32, 49-50, 54-57, 59-62, 65-68, 73-74, and 84-89 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,968,909 ("Agrawal"). Applicant respectfully disagrees.

Anticipation under 35 U.S.C. § 102 requires that a single piece of prior art discloses each and every element of the claimed invention, either expressly or inherently. *See In re Robertson,* 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999).

Agrawal teaches a method of *reducing* the immunostimulatory effects of phosphorothioate oligonucleotides used to treat pathogen-mediated disease states and other medical conditions. This is done by modifying at least one chemical structure within the oligonucleotide to produce a *decreased* immune response in an individual to which this

oligonucleotide is administered. The oligonucleotides of Agrawal may be combined with amphipathic agents, such as lipids, capable of producing a liposomal formulation in a therapeutic formulation. One example of a suitable amphipathic agent to be used in the liposomal formulation is saponin (see column 6, lines 26-29).

The Examiner contends that Agrawal teaches the claimed composition because the disclosed oligonucleotides are immunostimulatory (although less so than their unmodified counterpart) and can be mixed with saponin for liposomal delivery. There is no requirement that the saponin stimulates the immune response, and, in fact, immunostimulatory properties would be disfavored since the stated goal of Agrawal is to provide compositions with reduced immunostimulatory effects. In contrast, the present claims require that the saponin of the claimed compositions and methods be a saponin adjuvant. The Examiner points out that the term adjuvant is not limited to stimulating the immune response. In response, Applicant has amended the claims to further describe the saponin adjuvant as a saponin *immunostimulatory* adjuvant. Thus, it is clear that the effect referred to by the term adjuvant is the ability of the saponin to stimulate the immune response.

To serve the recited purpose of Agrawal, the saponins contemplated in Agrawal must be competent to form a liposome or micelle structure surrounding the oligonucleotide to perform the recited function in the therapeutic formulation. Not all saponins that form liposomes or micelles have antigenic activity. Because the stated purpose of the compositions of Agrawal is the reduction of immunogenicity, the saponins useful in the methods and compositions of Agrawal would preferably be those without adjuvant or immunostimulatory activity. For example, the saponins alfalfa hederagenin and Quinoa form liposome-like structures called ISCOMS but lack adjuvanticity (Bomford et al., 1992, *Vaccine* 10:572-577; submitted as Exhibit E to the Response filed January 18, 2002). Saponins lacking adjuvant activity would actually be considered preferable in Agrawal's method due to the ultimate goal of *decreasing* immunogenicity of the administered composition. Use of these non-adjuvant active saponins by Agrawal would not be encompassed by Applicant's claims due to the limitation of a *saponin adjuvant*.

Thus, Agrawal fails to explicitly disclose the claim limitation of a saponin *immunostimulatory* adjuvant. In the event that a reference does not explicitly teach all the elements of a claim, anticipation can only be shown by inherency if the cited reference makes clear that the missing descriptive matter is *necessarily* present in the thing described

in the reference and that it would be so recognized by one of ordinary skill in the art. *Continental Can Company USA, Inc. v. Monsanto Company*, 948 F.2d 1264 (Fed. Cir. 1991) (emphasis added). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). Substantial uncertainty regarding the existence of a product in the prior art, *i.e.*, uncertainty as to whether the inherent characteristic *necessarily* flows from the teaching of the prior art reference, is enough to preclude anticipation. *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983; *Bristol-Myers Co. v. USITC*, 15 USPQ2d 1258 (Fed. Cir. 1989). Because Agrawal does not explicitly teach all the elements of any present claim, and Applicant has proven that the missing descriptive matter is not *necessarily* present in the teaching of Agrawal, Agrawal fails to anticipate any present claim.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 102.

D. <u>Rejections Under 35 U.S.C. § 103</u>

Claims 19-27, 49-57, 59-68, 73-77, and 80-89 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner et al., 1997, *PNAS* 94:10833-10837 ("Weiner") in view of Kensil, 1996, *Critical Reviews in Therapeutic Drug Carrier Systems* 13:1-55 ("Kensil I"). According to the Examiner, Weiner discloses an immunostimulatory CpG motif oligonucleotide with the sequence of SEQ ID NO: 1, but does not disclose the combination of such immunostimulatory CpG motif oligonucleotide and a saponin. Kensil teaches the use of the saponin adjuvant QS-21 in combination with tumor antigens to enhance the immune response to said tumor antigen when administered to a subject. The Examiner contends that it would have been obvious to combine the two known adjuvants (the immunostimulatory CpG motif oligonucleotide with SEQ ID NO: 1 and QS-21), particularly in light of a teaching in Weiner that provides an invitation to experiment with combinations of immunostimulatory CpG motif oligonucleotides with other adjuvants. Applicant respectfully disagrees.

Claims 19-27, 49-57, 59-68, and 71-89 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu et al., 1997, *Journal of Experimental Medicine* 186:1623-1631 ("Chu") in view of Kensil I. According to the Examiner, Chu teaches administering phosphorothioate oligonucleotide 1826 or 1760 as an adjuvant to increase the IgG2a immune

response in a mouse. Phosphorothioate oligonucleotide 1826 or 1760 have unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2. The Examiner admits that there is no suggestion in Chu, however, to combine the phosphorothioate oligonucleotides with QuilA, QS-7, QS-17, QS-18, or QS-21. According to the Examiner, this deficiency of Chu is remedied by Kensil I, because Kensil I allegedly teaches the combination of Quil A, QS-7, QS-17, QS-18 or QS-21 with other adjuvants to increase the adjuvant effect. Applicant respectfully disagrees.

Assuming, *arguendo*, that the cited references did make a *prima facie* case of obviousness, Applicant has demonstrated the unexpected result of synergism of immunostimulatory CpG motif oligonucleotides and saponin adjuvants, thereby rebutting any *prima facie* case of obviousness. The Examiner agrees that Applicant has shown unexpected results with the specific combination of QS-21 and phosphorothioate oligonucleotides 1758 (page 17, lines 14-15 of the Office Action mailed July 26, 2001) and 1826 (page 14, lines 1-2 of the Office Action mailed February 12, 2002). The Examiner, however, questions the generalizablity of these results to the genus of immunostimulatory oligonucleotides comprising at least one unmethylated CpG motif and the genus of saponin immunostimulatory adjuvants.

In addition to oligonucleotides 1758 and 1826, Applicant submits that an additional oligonucleotide has been shown to have a synergistic immunostimulatory adjuvant activity in combination with QS-21. International Publication No. WO 00/62800 (submitted herewith as Reference AB and referred to herein as "Friede") used either oligonucleotide 2006 (comprising at least one unmethylated CpG motif), QS-21, or a combination of both as adjuvants to direct an immune response to the influenza HA antigen (Example 2 on pages 25-27). A synergistic effect was observed in the immune response when2006 and QS-21 were used in combination as compared with immune response seen with other alone. This can be seen by comparing bars B (2006 alone) and C (QS-21 alone) to bar D (the combination of 2006 and QS-21) of Figure 3 in Friede.

Furthermore, each of the three oligonucleotides demonstrated to have synergistic immune adjuvant activity when used in combination with QS-21 have different sequences. The common characteristic is that each has at least one unmethylated CpG motif. In fact, Weiner observed that when oligonucleotides with *methylated* CpG motifs but having identical sequences to the immunostimulatory oligonucleotides (having *unmethylated* CpG motifs) were used in immunizations, no antibody production was seen in response to antigen

(first full paragraph in column 2 on page 10836). Although there was variation in the degree of adjuvanticity for the different immunostimulatory oligonucleotides, each was an adjuvant none-the-less. Thus, although one might expect a *quantitative* difference between different oligonucleotides (*e.g.*, in the degree of synergism seen when used in combination with a saponin adjuvant), there is no indication that one would expect to see a *qualitative* difference between oligonucleotides (*e.g.*, in the ability to have at least some degree of synergism when used in combination with a saponin adjuvant). In fact, one of skill in the art would expect that the claimed CpGs share a mechanism of action, due to their shared CpG motif, and that they would all exhibit synergism when combined with a saponin adjuvant.

The Examiner further asserts that the genus of saponin immunostimulatory adjuvants is represented by one species (*i.e.*, QS-21). The present claims are limited to those saponins that are "saponin immunostimulatory" adjuvants. Therefore the claims do not encompass saponins which do not have immunostimulatory adjuvant activity. Applicant agrees that a combination of a non-adjuvant active saponin with an immunostimulatory oligonucleotide would not be expected to have the synergistic effect demonstrated in the instant specification. Applicant has discovered that adjuvant active saponins can be combined with immunostimulatory oligonucleotides for a synergistic effect. Thus, within the class of *adjuvant immunostimulatory saponins*, which includes Quil A, QS-7, QS-17, QS-18, and QS-21, one of ordinary skill in the art would expect each to have a synergistic effect when combined with an immunostimulatory oligonucleotide in light of the data presented in the instant specification. Thus, all of the combinations would be expected to produce adjuvant effects that are greater than simply additive.

Quil A, QS-7, QS-17, QS-18, and QS-21 are all saponins that are isolated from *Quillaja saponaria*. All are structurally very similar. When the monosaccharide composition of QS-7, QS-17, QS-18, and QS-21 was determined, all were found to be closely related (page 384 of Kensil et al,. 1993, "Novel Adjuvants from *Quillaja saponaria* Molina" in AIDS Research Reviews Volume 3 edited by Koffet al. New York; submitted herein as Reference AC; herein "Kensil II"). QS-18 has an additional glucose as compared to QS-21 while QS-17 has an additional rhamnose as compared to QS-18. Figure 2 of Kensil II shows the proposed structures of QS-17, QS-18, and QS-21 derived from comparison of monosaccharide composition and molecular weight. Additionally, all four saponins shared a highly complex glycoside component with the same linkages (second full paragraph on page 435, column 1 of Kensil et al., 1991, "Separation and Characterization of

Saponins with Adjuvant Activity from *Quillaja saponaria* Molina cortex" J. Immunol. 146:431; submitted herewith as Reference AD; herein "Kensil III"). Compared to the large portion of the structure that is identical, these differences are minor.

These minor differences do not appear to be in the portions of the molecule responsible for their immunostimulatory adjuvant activity. When compared to other adjuvants (*e.g.*, aluminum hydroxide, CFA, IFA, a mixture of monophosphoryl lipid A and trehalose dimycolate), each of the saponins caused a 10^3 increase in antigen specific IgG antibody titers (page 433, column 2, third full paragraph in Kensil III). In fact, the Examiner acknowledges that QS-7, QS-17, QS-18, and QS-21 all have equivalent adjuvant effects (page 14, lines 18-19 of the Office Action mailed July 26, 2001).

Although there are differences in some aspects of the saponins, they are generally not correlated with their adjuvanticity. For example, Kensil II (on page 387, the first full paragraph) reports that adjuvant active saponins had a wide range of toxicity as assayed by lethality in mice. No correlation existed, however, between toxicity and adjuvanticity (*i.e.*, both toxic and non-toxic saponins acted as immunostimulatory adjuvants). Additionally, QS-7 is a poor detergent as revealed by its non-hemolytic properties yet has adjuvant characteristics similar to those of saponins that are highly hemolytic (*e.g.*, QS-17, QS-18, and QS-21) (page 436, column 1, lines 13-18 of Kensil III).

Furthermore, data regarding an additional saponin, β-escin, is disclosed in Friede and demonstrates that β-escin and oligonucleotide 1826[1] act synergistically for enhancing an antibody response to an antigen (Example 3 on pages 27-28). This can be seen by comparing bars B (1826 alone) and C (β-escin alone) to bar D (the combination of 1826 and β-escin) of Figure 5 in Friede.

Applicant believes that because of the functional similarity of the immunostimulatory saponin adjuvants, the claimed genus is supported by the demonstrated data. The Court of Customs and Patent Appeals stated (In re *Kollman*, 595 F.2d 48:

> We feel that the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof. The proof, thus

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1 The oligonucleotide nomenclature of Friede differs from that of the instant specification. A comparison of the disclosed sequence for Friede's 2006 revealed that is identical to 1826 in the instant specification.

considered, might then be sufficient to rebut a PTO holding of prima facie obviousness.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 103.

STATEMENT UNDER 37 C.F.R. § 1.607(c)

Applicant has presented claims which correspond exactly or substantially to claims 1-11 of United States Patent No. 6,406,705, issued June 18, 2002, a copy of which is submitted herewith as reference AA in the accompanying Supplemental Information Disclosure Statement.

CONCLUSION

Applicant respectfully requests that the amendments and remarks above be entered and made of record in the file history of the instant application. Applicant believes that each ground for rejection has been successfully overcome or obviated and that the application is in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

Date: September 16, 2002

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Enclosure

25. The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide [is modified] comprises one or more non-traditional nucleotides.

26. The immune adjuvant composition as claimed in claim 25, wherein at least one of the [immunostimulatory oligonucleotide] one or more non-traditional nucleotides is [modified with at least one] a phosphorothioate-modified nucleotide.

63. An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the saponin adjuvant comprises substantially pure QS-7, QS-17 or QS

64. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 63.

65. An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide [is modified] comprises one or more non-traditional nucleotides.

66. The immune adjuvant composition as claimed in claim 65, wherein at least one of the [immunostimulatory oligonucleotide] one or more non-traditional nucleotides is [modified with at least one] a phosphorothioate-modified nucleotide.

67. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 65.

68. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 66.

69. An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

70. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 69.

71. An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

72. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 71.

73. An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide [, wherein said immunostimulatory oligonucleotide is from 4-40 base pairs in length,] comprising at least one

unmethylated CpG motif, wherein said immunostimulatory oligonucleotide is 4-40 bases in length.

74. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 73.

75. An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif;

wherein the saponin adjuvant is a [chemically modified] non-traditional saponin adjuvant.

76. A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 75.

77. The [method] composition of claim 19, wherein the saponin adjuvant is a [chemically modified] non-traditional saponin adjuvant.

80. The immune adjuvant composition as claimed in claim 19, wherein the composition increases the immune response to an antigen encoded by a nucleic acid when administered to an individual.

19. An immune adjuvant composition comprising

(a) a saponin ~~immunostimulatory~~ adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide is not a part of a DNA vaccine vector.

20. The immune adjuvant composition as claimed in claim 19, wherein the saponin adjuvant is derived from *Quillaja saponaria*.

21. The immune adjuvant composition as claimed in claim 20, wherein the saponin adjuvant comprises a substantially pure saponin adjuvant.

22. The immune adjuvant composition as claimed in claim 21, wherein the substantially pure saponin adjuvant comprises QS-7, QS-17, QS-18, or QS-21.

23. The immune adjuvant composition as claimed in claim 22, wherein the substantially pure saponin adjuvant comprises QS-21.

24. The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

25. (amended) The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises one or more non-traditional nucleotides.

26. (amended) The immune adjuvant composition as claimed in claim 25, wherein at least one of the one or more non-traditional nucleotides is a phosphorothioate-modified nucleotide.

27. The immune adjuvant composition as claimed in claim 19, wherein the immunostimulatory oligonucleotide comprises a CpG motif having the formula 5'X1CGX23', wherein X1 is adenine, guanine, or thymine, and X2 is cytosine, thymine, or adenine.

28. The immune adjuvant composition as claimed in claim 27, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

63. (amended) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the saponin adjuvant comprises substantially pure QS-7, QS-17 or QS-18.

64. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 63.

65. (amended) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises one or more non-traditional nucleotides.

66. (amended) The immune adjuvant composition as claimed in claim 65, wherein at least one of the one or more non-traditional nucleotides is a phosphorothioate-modified nucleotide.

67. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid

encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 65.

68. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 66.

69. (amended) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1).

70. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 69.

71. (amended) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif,

wherein the immunostimulatory oligonucleotide comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

72. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 71.

73. (amended) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif, wherein said immunostimulatory oligonucleotide is 4-40 bases in length.

74. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 73.

75. (amended) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant; and

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif;

wherein the saponin adjuvant is a non-traditional saponin adjuvant.

76. (amended) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 75.

77. (amended) The composition of claim 19, wherein the saponin adjuvant is a non-traditional saponin adjuvant.

78. The immune adjuvant composition as claimed in claim 27, wherein the CpG motif comprises TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

80. (amended) The immune adjuvant composition as claimed in claim 19, wherein the composition increases the immune response to an antigen encoded by a nucleic acid when administered to an individual.

81. The immune adjuvant composition as claimed in claim 80, wherein the individual is a mammal.

82. The immune adjuvant composition as claimed in claim 80, wherein the individual is a human.

83. The immune adjuvant composition as claimed in claim 80, wherein the individual is an animal.

90. (new) A method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition as claimed in claim 19.

91. (new) The method as claimed in claim 90, wherein the saponin adjuvant is derived from *Quillaja saponaria.*

92. (new) The method as claimed in claim 91, wherein the saponin adjuvant comprises a substantially pure saponin adjuvant.

93. (new) The method as claimed in claim 92, wherein the substantially pure saponin adjuvant comprises QS-7, QS-17, QS-18, or QS-21.

94. (new) The method as claimed in claim 93, wherein the substantially pure saponin adjuvant comprises QS-21.

95. (new) The method as claimed in claim 90, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

96. (new) The method as claimed in claim 90, wherein the immunostimulatory oligonucleotide comprises one or more non-traditional nucleotides.

97. (new) The method as claimed in claim 96, wherein at least one of the one or more non-traditional nucleotides is a phosphorothioate-modified nucleotide.

98. (new) The method as claimed in claim 90, wherein the immunostimulatory oligonucleotide comprises a CpG motif having the formula 5'X_1CG$X_2$3', wherein X_1 is adenine, guanine, or thymine, and X_2 is cytosine, thymine, or adenine.

99. (new) The method as claimed in claim 98, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1) or TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

100. (new) The method as claimed in claim 90, wherein the individual is an animal.

101. (new) The method as claimed in claim 100, wherein the animal is a mammal.

102. (new) The method as claimed in claim 101, wherein the individual is a human.

103. (new) An immune adjuvant composition comprising

(a) a saponin immunostimulatory adjuvant;

(b) an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif; and

(c) a nucleic acid molecule comprising a nucleotide sequence that encodes an antigen to which an immune response is desired,

wherein the immunostimulatory oligonucleotide is not a part of the nucleic acid molecule comprising the nucleotide sequence that encodes the antigen and the nucleotide sequence is operatively linked to a promoter.

104. (new) The immune adjuvant composition as claimed in claim 103, wherein the saponin adjuvant is derived from *Quillaja saponaria*.

105. (new) The immune adjuvant composition as claimed in claim104, wherein the saponin adjuvant comprises a substantially pure saponin adjuvant.

106. (new) The immune adjuvant composition as claimed in claim 105, wherein the substantially pure saponin adjuvant comprises QS-7, QS-17, QS-18, or QS-21.

107. (new) The immune adjuvant composition as claimed in claim 106, wherein the substantially pure saponin adjuvant comprises QS-21.

108. (new) The immune adjuvant composition as claimed in claim 103, wherein the immunostimulatory oligonucleotide comprises a CpG motif comprising more than one unmethylated CpG dinucleotide.

109. (new) The immune adjuvant composition as claimed in claim 103, wherein the immunostimulatory oligonucleotide comprises one or more non-traditional nucleotides.

110. (new) The immune adjuvant composition as claimed in claim 109, wherein at least one of the one or more non-traditional nucleotides is a phosphorothioate-modified nucleotide.

111. (new) The immune adjuvant composition as claimed in claim 103, wherein the immunostimulatory oligonucleotide comprises a CpG motif having the formula 5'X1CGX23', wherein X1 is adenine, guanine, or thymine, and X2 is cytosine, thymine, or adenine.

112. (new) The immune adjuvant composition as claimed in claim 111, wherein the CpG motif comprises TCTCCCAGCGTGCGCCAT (SEQ ID NO:1) or TCCATGACGTTCCTGACGTT (SEQ ID NO:2).

113. (new) The method of any of claims 64, 67, 68, 70, 72, 74, 76, or 77, wherein the nucleic acid encoding the antigen is administered to the individual or test system within 0-2 days of the administration of the immune adjuvant composition.

114. (new) The method of claim 113, wherein the nucleic acid encoding the antigen is administered to the individual or test system concurrently with the immune adjuvant composition.

115. (new) The method of claim 113, wherein the nucleic acid encoding the antigen is administered before the immune adjuvant composition.

116. (new) The method of claim 113, wherein the nucleic acid encoding the antigen is administered after the immune adjuvant composition.